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(54) EPOXIDES AND HALOHYDRINS AND CONVERSION THEREOF TO ALKANOLAMINE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new chemical process and more particularly it relates to a process for the manufacture of optically-active alkanolamine derivatives which have useful therapeutic properties.

It is known, for example from United Kingdom Patent Specifications Nos. 994,918; 995,800; 1,021,522; 1,023,214; 1,046,001; 1,047,927; 1,058,822; 1,066,613; 1,069,341; 1,069,342; 1,069,345; 1,079,989; 1,089,769; 1,123,258; 1,127,469; 1,128,052 and 1,129,072 that many 1 - amino - 3 - aryloxy - 2 - propanol derivatives and simple derivatives thereof possess β -adrenergic blocking properties, and are therefore useful in the treatment or prophylaxis of heart diseases such as angina pectoris and cardiac arrhythmias, and in the treatment of hypertension and phaeochromocytoma, in man.

It is also known that when such 1 - amino - 3 - aryloxy - 2 - propanol derivatives are resolved into their optically-active enantiomeric forms, some separation of the biological properties of the racemic compounds is effected. Thus in the case of 1 - isopropylamino - 3 - (1 - naphthyl) - 2 - propanol, also known as propranolol and "Inderal" ("Inderal" is a Registered Trade Mark), it has been shown that the (-) isomer is responsible for blocking isoprenaline-induced tachycardia in cats, dogs and humans, whereas the (+) isomer is almost inactive for this purpose, and that both the (-) and (+) isomers abolish cardiac arrhythmias induced in cats, dogs and humans by digitalis glycosides. Certain laevorotatory 1 - amino - 3 -

aryloxy - 2 - propanol derivatives, and a process for their manufacture which comprises resolving the corresponding racemic compounds, are described and claimed in United Kingdom Patent Specification No. 1,069,343; certain dextrorotatory 1 - amino - 3 - aryloxy - 2 - propanol derivatives, and processes for their manufacture which comprise either resolving the corresponding racemic compounds, or resolving *N*-benzyl derivatives of said racemic compounds and then removing the protecting *N*-benzyl radical, are described and claimed in United Kingdom Patent Specification No. 1,136,919.

The precise conditions of optically-active acid, solvent and temperature which are required to resolve any particular 1 - amino - 3 - aryloxy - 2 - propanol derivative must be worked out by tedious routine experiment for each individual 1 - amino - 3 - aryloxy - 2 - propanol derivative. We have now discovered, and herein lies our invention, that suitable precursors of 1 - amino - 2 - propanol side-chains may themselves be resolved, and that the optically-active intermediates thus obtained may be reacted with a wide range of phenols, naphthols and similar compounds to give optically-active 1 - amino - 3 - aryloxy - 2 - propanol derivatives, no substantial racemisation of the side-chain taking place during this process.

According to the invention we provide a process for the manufacture of optically-active alkanolamine derivatives of the formula:—



wherein R^1 stands for an alkyl, hydroxy-alkyl, aralkyl or cycloalkyl radical and wherein X stands for an aryl or benzo-fused heterocyclyl radical, either of which may

optionally be substituted, and the acid-addition salts thereof, which comprises the inter-

action of an optically-active epoxide or halohydrin of the formula:—



wherein R¹ has the meaning stated above, wherein R² stands for hydrogen or for an α-arylalkyl radical and wherein Z stands for a halogen atom, with a compound of the
10 formula:—



wherein X has the meaning stated above; whereafter if necessary the α-arylalkyl radical R² is removed by hydrogenolysis; and
15 whereafter if desired the product in free base form is reacted with an acid in order to form an acid-addition salt thereof.

As a suitable value for R¹ when it stands for an alkyl, hydroxyalkyl or aralkyl radical there may be mentioned, for example, an
20 alkyl radical of up to 6 carbon atoms, and preferably an alkyl radical of from 3 to 6 carbon atoms which is branched at the α-carbon atom, which alkyl radical may optionally be substituted by the hydroxy radical, or by a phenyl radical which may itself
25 optionally bear one or more halogen substituents or alkyl or alkoxy substituents each of up to 4 carbon atoms. Thus, a specific value for R¹ when it stands for an alkyl, hydroxy-
30 alkyl or aralkyl radical is, for example, the isopropyl, s-butyl, t-butyl, 2 - hydroxy - 1, 1 - dimethylethyl, 1,1 - dimethyl - 2 - phenylethyl, 1,1 - dimethyl - 3 - phenyl-
35 propyl or 3 - (4 - chlorophenyl) - 1,1 - dimethylpropyl radical.

As a suitable value for R¹ when it stands for a cycloalkyl radical there may be mentioned, for example, a cycloalkyl radical of
40 from 3 to 8 carbon atoms, for example the cyclopropyl, cyclobutyl or cyclopentyl radical.

As a suitable value for X when it stands for an optionally-substituted aryl radical there
45 may be mentioned, for example, a phenyl, naphthyl, anthryl, dihydroanthryl or fluorenyl radical which may optionally be substituted by one or more substituents selected from halogen atoms, for example fluorine, chlo-
50 rine, bromine and iodine atoms; alkyl, alkoxy and alkythio radicals, for example alkyl, alkoxy and alkythio radicals each of up to 10 carbon atoms, for example methyl, ethyl, isopropyl, n-butyl, t-butyl, t-amyl, methoxy,
55 ethoxy, isopropoxy, n-butoxy, isobutoxy, n-heptyloxy, methylthio and ethylthio radicals; alkylene radicals, for example alkylene radicals of 3 and 4 carbon atoms, for example trimethylene and tetramethylene radicals (that
60 is, for example, radicals which together with

the phenyl radical give indanyl or tetrahydronaphthyl radicals); acyl radicals, for example alkanoyl, aralkanoyl and aroyl radicals each of up to 10 carbon atoms, for example
65 acetyl, phenylacetyl and benzoyl radicals; hydroxyalkyl, halogenoalkyl and halogenoalkoxy radicals, for example hydroxyalkyl, halogenoalkyl and halogenoalkoxy radicals each of up to 5 carbon atoms, for example
70 hydroxymethyl, 2-hydroxyethyl, trifluoromethyl and 2,2 - dichloro - 1,1 - difluoroethoxy radicals; alkenyl, alkenyloxy, alkynyloxy and cycloalkoxy radicals, for example alkenyl, alkenyloxy, alkynyloxy and cycloalkoxy radicals each of up to 6 carbon
75 atoms, for example allyl, allvloxy, propargyloxy and cyclopentyloxy radicals; aryl, aryl-oxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl and aralkoxy radicals, for example, aryl, aryloxy, alkylaryloxy, arylthio,
80 arylsulphonyl, arylamino, aralkyl and aralkoxy radicals each of up to 10 carbon atoms, for example phenyl, phenoxy, 4-tolyloxy, phenylthio, phenylsulphonyl, anilino, benzyl, α,α-dimethylbenzyl and benzyloxy radicals; heterocyclyl radicals, for example simple and benzo-fused 5- and 6-membered heterocyclyl
85 radicals containing one or two hetero-atoms selected from nitrogen, oxygen and sulphur atoms, for example thienyl, thiazolyl, indolyl, benzoxazolyl, benzothiazolyl, quinolyl and quinoxaliny radicals; alkoxyalkyl radicals, for example alkyl radicals of up to 5 carbon atoms substituted by alkoxy radicals of up to
90 5 carbon atoms, for example methoxymethyl, ethoxymethyl and n-propoxymethyl radicals, alkoxy-carbonyl radicals, for example alkoxy-carbonyl radicals of up to 6 carbon atoms, for example methoxycarbonyl and ethoxycarbonyl radicals; alkylenedioxy radicals, for example
100 alkylenedioxy radicals of up to 4 carbon atoms, for example methylenedioxy, ethylenedioxy, trimethylene - 1,3 - dioxy and tetramethylene - 1,4 - dioxy radicals; and hydroxy, amino, cyano, carboxy and nitro radi-
105 cals.

As a suitable value for X when it stands for a benzo-fused heterocyclyl radical there may be mentioned, for example, a radical
110 formed by the fusion of a benzene ring to a 5- or 6-membered hetero-ring which contains one or two hetero-atoms selected from nitrogen, oxygen and sulphur atoms, which hetero-ring may contain one or more double-
115 bonds, and which benzo-fused heterocyclic radical may optionally bear one or more substituents selected from oxo radicals and those

substituents mentioned above as possible substituents in the aryl radical X, and which benzo-fused heterocyclic radical may optionally be fused to a second benzene ring. Thus, a suitable value for X when it stands for a benzo-fused heterocyclyl radical is, for example, an indolyl, benzofuranyl, 2,3 - dihydrobenzofuranyl, benzothienyl, quinolyl, chromanyl or xanthenyl radical, any of which may optionally bear one or two substituents in the hetero-ring selected from hydroxy and oxo radicals and alkyl radicals of up to 4 carbon atoms.

Preferred compounds which may be prepared by the process of the invention are those of the formula given above wherein R¹ stands for the isopropyl or t-butyl radical and wherein X stands for the 1-naphthyl or m-tolyl radical; or for a phenyl radical which bears a single substituent in the 2-position which is the phenyl radical or an alkyl, alkoxy, alkenyl, alkenyloxy, alkynyloxy, alkylthio or alkoxyalkyl radical each of up to 6 carbon atoms, especially the ethyl ethoxy, isopropoxy, allyl, allyloxy, propargyloxy, methylthio or methoxymethyl radical; or for the 4- or 5-indolyl radical or for a 1-alkyl-4- or 5-indolyl radical wherein the alkyl substituent contains up to 4 carbon atoms, for example the 1-methyl- or 1-ethyl-4- or 5-indolyl radical.

Suitable acid-addition salts of the optically-active alkanolamine derivatives which may be prepared by the process of the invention are, for example, salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates or sulphates, or salts derived from organic acids, for example oxalates, lactates, tartrates, acetates, salicylates,

citrates, benzoates, β-naphthoates, adipates or 1,1-methylene-bis-(2-hydroxy-3-naphthoates), or salts derived from acidic synthetic resins, for example sulphonated polystyrene resins, for example "Zeo-Karb" 225 ("Zeo-Karb" is a Trade Mark).

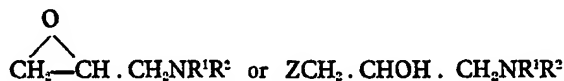
A suitable value for R² when it stands for an α-arylalkyl radical is, for example, the benzyl radical.

A suitable value for Z is, for example, the chlorine or bromine atom.

The process of the invention may be carried out in a diluent or solvent, for example methanol or ethanol, and it may be accelerated or completed by the application of heat, for example by heating to the boiling point of the diluent or solvent. The process may conveniently be carried out in the presence of an acid-binding agent, for example sodium hydroxide, or alternatively an alkali-metal derivative, for example the sodium or potassium derivative, of the compound of the formula X-AH, wherein X has the meaning stated above, may be used as starting material.

A compound wherein R² stands for an α-arylalkyl radical may be converted into the corresponding compound wherein R² stands for hydrogen by hydrogenolysis in the presence of a catalyst, for example a platinum or palladium-on-charcoal catalyst, in a diluent or solvent, for example ethanol. The hydrogenolysis may be carried out at ambient temperature and at atmospheric pressure or at a pressure of up to 100 atmospheres.

According to a further feature of the invention we provide the novel optically-active epoxides and halohydrins of the formula:—



wherein R¹, R² and Z have the meanings stated above, and the acid-addition salts thereof.

Particularly valuable epoxides of the invention are (+)-1,2-epoxy-3-isopropylaminopropane, (−)-1,2-epoxy-3-isopropylamino-propane, (+)-1,2-epoxy-3-t-butylaminopropane and (−)-1,2-epoxy-3-t-butylaminopropane, and the corresponding N-benzyl derivatives, and the acid-addition salts thereof.

Particularly valuable halohydrins of the invention are (+)-1-chloro-3-isopropylamino-2-propanol, (−)-1-chloro-3-isopropylamino-2-propanol, (+)-1-chloro-3-t-butylamino-2-propanol and (−)-1-chloro-3-t-butylamino-2-propanol, and the corresponding 1-bromo-derivatives, and the corresponding N-benzyl derivatives, and the acid-addition salts thereof.

Suitable acid-addition salts of the epoxides and halohydrins are those mentioned above as suitable salts of the optically-active alkanolamine derivatives prepared by the process of the invention, particularly hydrochlorides. Other suitable acid-addition salts of the epoxides and halohydrins are salts derived from optically-active acids which are used in the resolution process for the preparation of the optically-active epoxides and halohydrins as hereinafter described, particularly di-O-p-toluoyltartrates.

According to a further feature of the invention we provide a process for the manufacture of the optically-active epoxides and halohydrins of the invention, and the acid-addition salts thereof, which comprises the resolution of the corresponding racemic epoxide or halohydrin by conventional means using a suitable optically-active acid, whereafter if desired the resolved optically-active

acid-addition salt is converted into the corresponding optically-active free base.

A suitable optically-active acid which may be used in the resolution process of the invention is, for example, (+)- or (-)- di-*O* - *p* - toluoyltartaric acid, (+)- or (-)- di-*O* - benzoyltartaric acid; (+)- or (-)- tartaric acid, (+)- or (-)- camphor - 10 - sulphonic acid, or (+)- or (-)- 3 - bromo-camphor - 8 - sulphonic acid.

The resolution process of the invention may be carried out by reacting the racemic epoxide or halohydrin with the optically-active acid in an inert diluent or solvent, for example ether, in which the acid-addition salts are insoluble; isolating the mixture of diastereoisomeric acid-addition salts; fractionally crystallising the mixture of diastereoisomeric acid-addition salts from a suitable solvent, for example an alcohol, for example isopropanol, until each of the two diastereoisomeric acid-addition salts is substantially free from the other diastereoisomeric acid-addition salt; and, if desired, recovering the optically-active epoxide or halohydrin in free base form from the acid-addition salt thereof by conventional means.

The invention is illustrated but not limited by the following Examples:—

EXAMPLE 1

15 ml. of aqueous 2N-sodium hydroxide solution are added to a solution of 27.36 g. of (+)- 1 - chloro - 3 - isopropylamino - 2 - propanol hydrochloride in 450 ml. of water, 150 g. of sodium chloride are added and the mixture is extracted 4 times with 300 ml. of ether each time. The combined ethereal extracts are dried over anhydrous magnesium sulphate and the dried solution is added to a solution of 69.6 g. of (-)- di-*O* - *p* - toluoyltartaric acid in 200 ml. of ether. The mixture is filtered and the solid residue is crystallised from isopropanol. The mother liquor from this crystallisation is retained for use as described in Example 2, and the crystallised solid is recrystallised four times from isopropanol. There is thus obtained (+)- 1 - chloro - 3 - isopropylamino - 2 - propanol (-)- di-*O* - *p* - toluoyltartrate.

0.5 G. of the finally crystallised product is added to 20 ml. of aqueous 2N-sodium hydroxide solution and the mixture is extracted twice with 25 ml. of ether each time. The combined ethereal extracts are dried over anhydrous magnesium sulphate and ethereal hydrogen chloride solution is added to the dried solution. The mixture is filtered and the solid residue is washed with ether. There is thus obtained (+)- 1 - chloro - 3 - isopropylamino - 2 - propanol hydrochloride, m.p. 106°C., $[\alpha]_D^{25} = +25.9^\circ$ (c, 2.0% in ethanol).

EXAMPLE 2

The isopropanol mother liquor from the first crystallisation described in Example 1 is allowed to stand for 6 months and is then filtered. The filtrate is evaporated to dryness under reduced pressure and the residue is stirred with 50 ml. of aqueous N-sodium hydroxide solution. The mixture is extracted twice with 30 ml. of ether each time and the combined ethereal extracts are dried over magnesium sulphate. Ethereal hydrogen chloride solution is added to the dried solution and the mixture is filtered. The solid residue is crystallised from a mixture of 2 parts of isopropanol and 8 parts of ether and there is thus obtained (-)- 1 - chloro - 3 - isopropylamino - 2 - propanol hydrochloride, m.p. 106—108°C., $[\alpha]_D^{25} = -28.2^\circ$ (c, 3.8% in ethanol).

EXAMPLE 3

A mixture of 0.7 g. of 1-naphthol, 50 ml. of ethanol, 2.5 g. of (+)- 1 - chloro - 3 - isopropylamino - 2 - propanol (-)- di-*O* - *p* - toluoyltartrate, 0.6 g. of sodium hydroxide and 5 ml. of water is heated under reflux for 3 hours. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in ether and the solution is acidified with ethereal hydrogen chloride solution. The mixture is filtered and the solid residue is crystallised from a mixture of ether and ethanol. There is thus obtained (+)- 1 - isopropylamino - 3 - (1 - naphthoxy) - 2 - propanol hydrochloride, m.p. 190—192°C., $[\alpha]_D^{25} = +29.8^\circ$ (c, 0.442% in ethanol).

EXAMPLE 4

A mixture of 0.15 g. of 1-naphthol, 0.19 g. of (-)- 1 - chloro - 3 - isopropylamino - 2 - propanol hydrochloride, 20 ml. of ethanol, 0.08 g. of sodium hydroxide and 1 ml. of water is heated under reflux for 3 hours. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is stirred with a mixture of 10 ml. of aqueous N-hydrochloric acid and 10 ml. of ether and the aqueous acidic phase is separated and basified with 10 ml. of aqueous 2N-sodium hydroxide solution. The mixture is extracted with 25 ml. of ethyl acetate and the ethyl acetate extract is dried over anhydrous magnesium sulphate. Ethereal hydrogen chloride solution is added to the dried extract and the resulting solution is decanted from the oil which separates out immediately and is kept at ambient temperature for 18 hours. The mixture is filtered and the solid residue is washed with ether. There is thus obtained (-)- 1 - isopropylamino - 3 - (1 - naphthoxy) - 2 - propanol hydrochloride, m.p. 192°C., $[\alpha]_D^{25} = -28.3^\circ$ (c, 0.27% in ethanol).

EXAMPLE 5

A mixture of 0.54 g. of *m*-cresol, 2.7 g. of (+) - 1 - chloro - 3 - isopropylamino - 2 - propanol (—) - di - *O* - *p* - toluoyltartrate, 45 ml. of ethanol. 0.8 g. of sodium hydroxide and 1 ml. of water is heated under reflux for 6 hours. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is stirred with 25 ml. of aqueous *N*-hydrochloric acid and 25 ml. of ether and the aqueous phase is separated and basified with 25 ml. of aqueous 2*N*-sodium hydroxide solution. The mixture is extracted with 25 ml. of ethyl acetate and the ethyl acetate is dried over anhydrous magnesium sulphate. Ethereal hydrogen chloride solution is added to the dried extract, the mixture is filtered and the solid residue is crystallised from ethyl acetate. There is thus obtained (+) - 1 - isopropylamino - 3 - (3 - tolyloxy) - 2 - propanol hydrochloride, m.p. 114—116°C., $[\alpha]_D^{20} = +20.5^\circ$ (c, 2.03% in ethanol).

EXAMPLE 6

The procedure described in Example 5 is repeated except that 0.7 g. of *o*-ethoxyphenol is used in place of the *m*-cresol. There is thus obtained (+) - 3 - (2 - ethoxyphenoxy) - 1 - isopropylamino - 2 - propanol hydrochloride, crystallised from a mixture of equal volumes of ethyl acetate and ether, m.p. 49—50°C., $[\alpha]_D^{20} = +13.8^\circ$ (c, 2.33% in ethanol).

EXAMPLE 7

The procedure described in Example 5 is repeated on twice the scale, except that 1.74 g. of 4 - methoxy - 1 - naphthol are used in place of the *m*-cresol. There is thus obtained (+) - 1 - isopropylamino - 3 - (4 - methoxy - 1 - naphthoxy) - 2 - propanol hydrochloride, crystallised from ethanol, m.p. 166—168°C., $[\alpha]_D^{20} = +17.5^\circ$ (c, 1.38% in ethanol).

EXAMPLE 8

A solution of 2.4 g. of 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - chloro - 2 - propanol in 5 ml. of ethanol is added to a solution of 1.8 g. of (—) - di - *O* - *p* - toluoyltartaric acid in 5 ml. of ethanol and the mixture is kept at −20°C. for 72 hours. The mixture is filtered and the solid residue is washed with ethanol. There is thus obtained (—) - 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - chloro - 2 - propanol (—) - di - *O* - *p* - toluoyltartrate, m.p. 84°C. with decomposition, $[\alpha]_D^{20} = -41.7^\circ$ (c, 3.99% in ethanol). A sample of the abovementioned salt is converted into its free base by conventional means, and there is thus obtained (—) - *N* - benzyl - *N* - isopropylamino - 3 - chloro - 2 - propanol as an oil, $[\alpha]_D^{20} = -13.4^\circ$ (c, 10.27% in ethanol).

The 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - chloro - 2 - propanol used as starting material may be prepared as follows:—

A mixture of 75 g. of *N*-benzylisopropylamine, 39 ml. of epichlorohydrin and 200 ml. of methanol is stirred at ambient temperature for 18 hours. The mixture is evaporated to dryness under reduced pressure and the residue is distilled under high vacuum. There is thus obtained 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - chloro - 2 - propanol, b.p. 130—132°C./0.3 mm.

EXAMPLE 9

A mixture of 0.7 g. of α -naphthol, 40 ml. of ethanol, 4 ml. of water, 0.8 g. of sodium hydroxide and 3.1 g. of (—) - 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - chloro - 2 - propanol (—) - di - *O* - *p* - toluoyltartrate is heated under reflux for 3 hours. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is stirred with 10 ml. of aqueous 2*N*-sodium hydroxide solution and the mixture is extracted twice with 10 ml. of ether each time. The combined ethereal extracts are dried over anhydrous magnesium sulphate and filtered and the filtrate is added to a solution of 2.0 g. of (—) - di - *O* - *p* - toluoyltartaric acid in 15 ml. of methanol. The mixture is cooled and filtered. The solid residue consists of (—) - 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - (1 - naphthoxy) - 2 - propanol (—) - di - *O* - *p* - toluoyltartrate, m.p. 118—120°C. with decomposition, $[\alpha]_D^{20} = -45.08^\circ$ (c, 2.82% in dimethylformamide).

The (—) - 1 - (*N* - benzyl - *N* - isopropylamino) - 3 - (1 - naphthoxy) - 2 - propanol free base may be isolated from the abovementioned salt by conventional means, and said free base may be hydrogenolysed as described in Example 1 of United Kingdom Specification No. 1,136,919. There is thus obtained (+) - 1 - isopropylamino - 3 - (1 - naphthoxy) - 2 - propanol.

EXAMPLE 10

A solution of 2.5 g. of 1 - (*N* - benzyl - *N* - *t* - butylamino) - 3 - chloro - 2 - propanol in 5 ml. of ethanol is added to a solution of 1.8 g. of (—) - di - *O* - *p* - toluoyltartaric acid in 5 ml. of ethanol and the mixture is kept at −20°C. for 18 hours. The mixture is filtered and the solid residue is washed with ethanol. There is thus obtained (—) - 1 - (*N* - benzyl - *N* - *t* - butylamino) - 3 - chloro - 2 - propanol hydrogen (—) - di - *O* - *p* - toluoyltartrate, m.p. 184—185°C., $[\alpha]_D^{20} = -84.98^\circ$ (c, 3.24% in dimethylformamide).

The 1 - (*N* - benzyl - *N* - *t* - butylamino) - 3 - chloro - 2 - propanol used as

starting material may be prepared as follows:—

- 5 A mixture of 32.6 g. of *N* - benzyl - *t* - butylamine, 23.4 ml. of epichlorohydrin and 200 ml. of methanol is stirred at ambient temperature for 18 hours. The mixture is evaporated to dryness under reduced pressure and the residue is distilled under high vacuum. There is thus obtained 1 - (N - benzyl - *N* - *t* - butylamino) - 3 - chloro - 2 - propanol, b.p. 122—124°C./0.4 mm.

WHAT WE CLAIM IS:—

1. A process for the manufacture of optically-active alkanolamine derivatives of the

formula:—



wherein R^1 stands for an alkyl, hydroxyalkyl, aralkyl or cycloalkyl radical and wherein X stands for an aryl or benzo-fused heterocyclyl radical, either of which may optionally be substituted, and the acid-addition salts thereof which comprises the interaction of an optically-active epoxide or halohydrin of the formula:—



- wherein R^1 has the meaning stated above, wherein R^2 stands for hydrogen or, for an α -arylalkyl radical and wherein Z stands for a halogen atom, with a compound of the formula:—



- wherein X has the meaning stated above; whereafter is necessary the α -arylalkyl radical R^2 is removed by hydrogenolysis; and whereafter if desired the product in free base form is reacted with an acid in order to form an acid-addition salt thereof.

2. A process as claimed in claim 1 wherein in the starting materials R^1 stands for an alkyl radical of from 3 to 6 carbon atoms which is branched at the α -carbon atom, which alkyl radical may optionally be substituted by the hydroxy radical, or by a phenyl radical which may itself optionally bear one or more halogen substituents or alkyl or alkoxy substituents each of up to 4 carbon atoms, or wherein R^1 stands for a cycloalkyl radical of from 3 to 8 carbon atoms; wherein R^2 stands for hydrogen or for the benzyl radical; wherein Z stands for the chlorine or bromine atom; and wherein X stands for a phenyl, naphthyl, anthryl, dihydroanthryl or fluorenyl radical which may optionally be substituted by one or more substituents selected from halogen atoms, alkyl, alkoxy and alkylthio radicals each of up to 10 carbon atoms, alkylene radicals of 3 and 4 carbon atoms, alkanoyl, aralkanoyl and aroyl radicals each of up to 10 carbon atoms, hydroxyalkyl, halogenoalkyl and halogenoalkoxy radicals each of up to 5 carbon atoms, alkenyl, alkenyloxy, alkyloxy and cycloalkoxy radicals each of up to 6 carbon atoms, aryl, aryloxy, alkylaryloxy, arylthio, arylsulphonyl, arylamino, aralkyl and aralkoxy radicals each of up to 10 carbon atoms, simple and benzo-fused 5- and 6-membered heterocyclyl radicals containing one or two

hetero-atoms selected from nitrogen, oxygen and sulphur atoms, alkyl radicals of up to 5 carbon atoms substituted by alkoxy radicals of up to 5 carbon atoms, alkoxycarbonyl radicals of up to 6 carbon atoms, alkylendioxy radicals of up to 4 carbon atoms, and hydroxy, amino, cyano, carboxy and nitro radicals, or wherein X stands for a radical formed by the fusion of a benzene ring to a 5- or 6-membered hetero-ring which contains one or two hetero-atoms selected from nitrogen, oxygen and sulphur atoms, which hetero-ring may contain one or more double-bonds, and which benzo-fused heterocyclic radical may optionally bear one or more substituents selected from oxo radicals and those substituents mentioned above as possible substituents in the phenyl, naphthyl, anthryl, dihydroanthryl or fluorenyl radical X, and which benzo-fused heterocyclic radical may optionally be fused to a second benzene ring.

3. A process as claimed in claim 2 wherein in the starting materials R^1 stands for the isopropyl, *s*-butyl, *t*-butyl, 2 - hydroxy - 1,1 - dimethylethyl, 1,1 - dimethyl - 2 - phenylethyl, 1,1 - dimethyl - 3 - phenylpropyl, 3 - (4 - chlorophenyl) - 1,1 - dimethylpropyl, cyclopropyl, cyclobutyl or cyclopentyl radical, and wherein X stands for a phenyl, naphthyl, anthryl, dihydroanthryl or fluorenyl radical which may optionally be substituted by one or more substituents selected from fluorine, chlorine, bromine and iodine atoms and methyl, ethyl, isopropyl, *n*-butyl, *t*-butyl, *t*-amyl, methoxy, ethoxy, isopropoxy, *n*-butoxy, isobutoxy, *n*-heptyloxy, methylthio, ethylthio, trimethylene, tetramethylene, acetyl, phenylacetyl, benzoyl, hydroxymethyl, 2-hydroxyethyl, trifluoromethyl, 2,2 - dichloro - 1,1 - difluoroethoxy, allyl, allyloxy, propargyloxy, cyclopentyloxy, phenyl, phenoxy, 4-tolyloxy, phenylthio, phenylsulphonyl, anilino, benzyl, α,α -dimethylbenzyl, benzyloxy, thienyl, thiazolyl, indolyl, benzo-oxazolyl, zenzothiazolyl, quinolyl, quinox-

linyl, methoxymethyl, ethoxymethyl, n-propoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylenedioxy, ethylenedioxy, trimethylene - 1,3 - dioxy, tetramethylene - 1,4 - dioxy, hydroxy, amino, cyano, carboxy and nitro radicals, or wherein X stands for an indolyl, benzofuranyl, 2, 3- dihydrobenzofuranyl, benzothienyl, quinolyl, chromanyl or xanthenyl radical any of which may optionally bear one or two substituents in the hetero-ring selected from hydroxy and oxo radicals and alkyl radicals of up to 4 carbon atoms.

4. A process as claimed in claim 3 wherein in the starting materials R¹ stands for the isopropyl or t-butyl radical and X stands for the 1-naphthyl or m-tolyl radical; or for a phenyl radical which bears a single substituent in the 2-position which is the phenyl radical or an alkyl, alkoxy, alkenyl, alkenyloxy, alkynyloxy, alkylthio or alkoxyalkyl radical each of up to 6 carbon atoms, or for the 4- or 5- indolyl radical or for a 1 - alkyl - 4 - or 5-indolyl radical wherein the alkyl substituent contains up to 4 carbon atoms.

5. A process as claimed in claim 4 wherein in the starting materials X stands for a phenyl radical which bears a single substituent in the 2-position which is the ethyl, ethoxy, isopropoxy, allyl, allyloxy, propargyloxy, methylthio or methoxymethyl radical, or X stands for the 1 - methyl - or 1 - ethyl - 4 - or 5-indolyl radical.

6. A process as claimed in any of claims 1 to 5 wherein the product in free base form is reacted with an acid in order to form the hydrochloride, hydrobromide, phosphate, sulphate, oxalate, lactate, tartrate, ace-

rate, salicylate, citrate, benzoate, β-naphthoate, adipate or 1,1 - methylene - bis - (2 - hydroxy - 3 - naphthoate) thereof, or wherein it is reacted with a sulphonated polystyrene resin.

7. A process as claimed in any of claims 1 to 6 which is carried out in a diluent or solvent.

8. A process as claimed in any of claims 1 to 7 which is accelerated or completed by the application of heat.

9. A process as claimed in any of claims 1 to 8 which is carried out in the presence of an acid-binding agent or wherein an alkalimetal derivative of the compound of the formula X—OH, wherein X has any of the meanings stated in any of claims 1 to 5, is used as starting material.

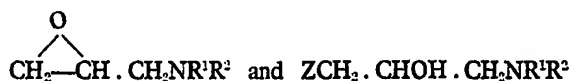
10. A process as claimed in any of claims 1 to 9 wherein compound wherein R² stands for an α-arylalkyl radical is converted into the corresponding compound wherein R² stands for hydrogen by hydrogenolysis in the presence of a catalyst and in a diluent or solvent.

11. A process as claimed in claim 10 wherein the catalyst is platinum or palladium-on-charcoal and wherein the diluent or solvent is ethanol.

12. A process as claimed in any of claims 1 to 4 and 6 to 9 substantially as hereinbefore described in Examples 3 and 4.

13. A process as claimed in any of claims 1 to 11 substantially as hereinbefore described in Examples 5, 6, 7 and 9.

14. Optically-active epoxides and halohydrins of the formula:—



wherein R¹, R² and Z have the meaning stated in claim 1, and the acid-addition salts thereof.

15. Optically-active epoxides and halohydrins as claimed in claim 14 wherein R¹, R² and Z have the meanings stated in claim 2.

16. Optically-active epoxides and halohydrins as claimed in claim 15 wherein R¹ has the meaning stated in claim 3.

17. The compounds (+) - 1,2 - epoxy - 3 - isopropylaminopropane, (—) - 1,2 - epoxy - 3 - isopropylaminopropane, (+) - 1,2 - epoxy - 3 - t - butylamino - propane and (—) - 1,2 - epoxy - 3 - t - butylamino - propane, and the corresponding N - benzyl derivatives, and the acid-addition salts thereof.

18. The compounds (+) - 1 - chloro - 3 - isopropylamino - 2 - propanol, (—) - 1 - chloro - 3 - isopropylamino - 2 - propanol, (+) - 1 - chloro - 3 - t - butyl-

amino - 2 - propanol and (—) - 1 - chloro - 3 - t - butylamino - 2 - propanol, and the corresponding 1 - bromo - derivatives, and the corresponding N - benzyl derivatives, and the acid-addition salts thereof.

19. Acid-addition salts as claimed in any of claims 14 to 18 which are hydrochlorides, hydrobromides, phosphates, sulphates, oxalates, lactates, tartrates, acetates, salicylates, citrates, benzoates, β-naphthoates, adipates or 1,1 - methylene - bis - (2 - hydroxy - 3 - naphthoates), or salts derived from sulphonated polystyrene resins, or salts derived from (+) - or (—) - di - O - p - toluoyl-tartaric acid, (+) - or (—) - di - O - benzoyltartaric acid; (+) - or (—) - tartaric acid, (+) - or (—) - camphor - 10 - sulphonic acid, or (+) - or (—) - 3 - bromocamphor - 8 - sulphonic acid.

20. The compound (+) - 1 - chloro - 3 - isopropylamino - 2 - propanol and the hy-

drochloride and the (—) - di - O - p - toluoyltartrate thereof.

21. The compound (—) - 1 - chloro - 3 - isopropylamino - 2 - propanol and the hydrochloride thereof.

22. The compound (—) - 1 - (N - benzyl - N - isopropylamino) - 3 - chloro - 2 - propanol and the (—) - di - O - p - toluoyltartrate thereof.

23. The compound (—) - 1 - (N - benzyl - N - t - butylamino) - 3 - chloro - 2 - propanol and the hydrogen (—) - di - O - p - toluoyltartrate thereof.

24. A process for the manufacture of the optically-active epoxides and halohydrins and the acid-addition salts thereof, claimed in any of claims 14 to 23, which comprises the resolution of the corresponding racemic epoxide or halohydrin by conventional means using a suitable optically-active acid, whereafter if desired the resolved optically-active acid-addition salt is converted into the corresponding optically-active free base.

25. A process as claimed in claim 24 wherein the optically-active acid is (+)- or (—) - di - O - p - toluoyltartaric acid, (+)- or (—) - di - O - benzoyltartaric acid; (+)- or (—) - tartaric acid, (+) or (—) - camphor - 10 - sulphonic acid, or (+)- or (—) - 3 - bromocamphor - 8 - sulphonic acid.

26. A process as claimed in claim 24 or 25 which is carried out by reacting the racemic epoxide or halohydrin with the optically-active acid in an inert diluent or solvent in which the acid-addition salts are insoluble; isolating the mixture of diastereoisomeric acid-addition salts; fractionally crystallising the mixture of diastereoisomeric acid-addition salts from a suitable solvent until each of the two diastereoisomeric acid-addition salts is substantially free from the other diastereoisomeric acid-addition salt; and, if desired, recovering the optically-active epoxide or halohydrin in free base form from the acid-addition salt thereof by conventional means.

27. Optically-active halohydrins and acid-addition salts thereof, claimed in any of claims 14 to 16 and 18 to 21, and a process for their manufacture, claimed in any of claims 24 to 26, substantially as hereinbefore described in Examples 1 and 2.

28. Optically-active halohydrins and acid-addition salts thereof, claimed in any of claims 14, 15, 16, 18, 19, 22 and 23, and a process for their manufacture, claimed in any of claims 24 to 26, substantially as hereinbefore described in Examples 8 and 10.

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